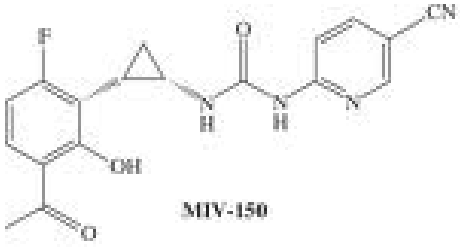
Communications Working Groups Meeting

HIV Prevention and MPT Product Pipeline Update

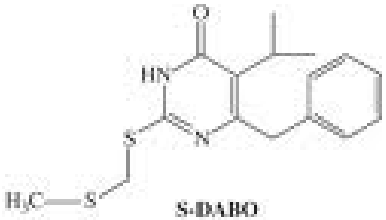
J. Romano

April 3, 2013

Part 1:
New ARV and HIV Prevention Products and Strategies



MIV-150



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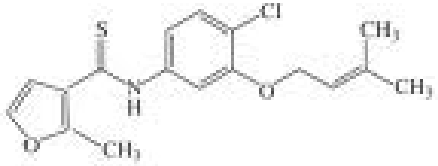

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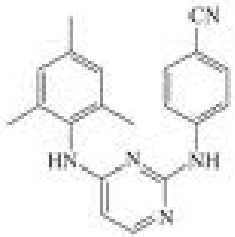


TMC-120

Oral PrEP Study Results

Study	Product	Population	Efficacy Result
iPREX	Truvada, daily	MSM	44%, p=0.005 95% CI 15-63%
Partners PrEP	Truvada, daily	Serodiscordant Couples	62%, p=0.0003 95% CI 34-78%
	TDF, 300 mg daily		73%, p<0.0001 95% CI 49-85%
TDF2	Truvada, daily	HIV- women and men	63%, p=0.013 95% CI 22-83%
FEM PrEP	Truvada, daily	HIV- women	No Effect
VOICE	Truvada, daily	HIV- women	Early Termination
	TDF, 300 mg daily		Early Termination

HPTN 069

PHASE II RANDOMIZED, DOUBLE-BLIND, STUDY OF SAFETY AND TOLERABILITY OF MARAVIROC, MARAVIROC + EMTRICITABINE, MARAVIROC + TENOFOVIR OR TENOFOVIR + EMTRICITABINE FOR PREEXPOSURE PROPHYLAXIS TO PREVENT HIV TRANSMISSION IN AT-RISK MEN WHO HAVE SEX WITH MEN AND IN AT-RISK WOMEN NEXT-PREP: NOVEL EXPLORATION OF THERAPEUTICS FOR PREP

4 Arms:

MVC 300 mg + FTC placebo + TDF Placebo each daily

MVC 300 mg + FTC 200 mg + TDF Placebo each daily

MVC + FTC Placebo + TDF 300 mg each daily

MVC placebo + FTC 200 mg + TDF 300 mg each daily

Population: 400 men, 200 women: uninfected, at-risk, 48 wks product use

1º Objective: Safety- grade 3 or higher AEs

2º Objectives: Safety; blood compartment PK; tissue drug levels; DDI; acceptability; sexual behaviors; quality of life

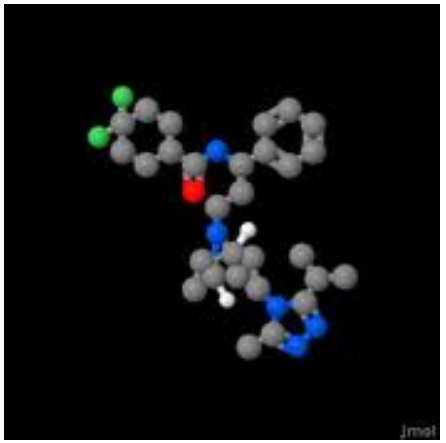
Topical ARV PrEP Studies

Study	Product	Population	Efficacy Result
CAPRISA 004	1% TFV gel, BAT 24	HIV- women	39%, p=0.017 95% CI 6-69%

Study	Product	Population	Results
FACTS 001	1% TFV Gel BAT 24	2900 HIV- women (1:1), 18-40 yrs	2015
ASPIRE	Dapivirine IVR 25 mg	3476 HIV- women (1:1)18-45 yrs	2015
The Ring Study	Dapivirine IVR 25 mg	1650 HIV- women (2:1) 18-45 yrs	2015

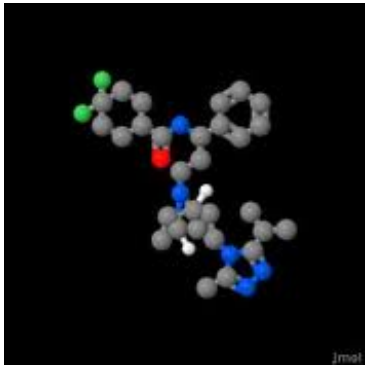
MTN 013:
Phase 1 safety and pharmacokinetics of dapivirine/maraviroc vaginal ring

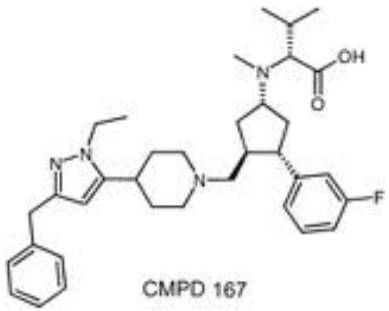
- First combination ARV topical prevention product; first entry blocker
- Silicone matrix ring configuration
- 4 arms, 12 women per arm:
  - Dapivirine only, maraviroc only, dapivirine-maraviroc combination, placebo
- 28 day use
- Endpoints: Safety, pharmacokinetics, tissue compartment drug levels
- Pharmacodynamics assessment via ex vivo challenge of day 28 post dosing biopsies
- Follow up complete; final data analysis ongoing



Other ARV Vaginal Rings in Development

- Maraviroc and CMPD 167 silicone matrix IVRs
  - Malcolm et al 2012
  - In vitro characterization and macaque safety/release
- MC1220 (NNRTI) silicone matrix IVR
  - Fetherston et al 2013
  - Macaque safety, release and efficacy
- MIV-150 (NNRTI) silicone matrix IVR
  - Singer et al 2012
  - In vitro; macaque release and efficacy
- MIV-160 (NNRTI) EVA matrix IVR
  - Aravantinou et al., 2012
  - In vitro; macaque release and efficacy

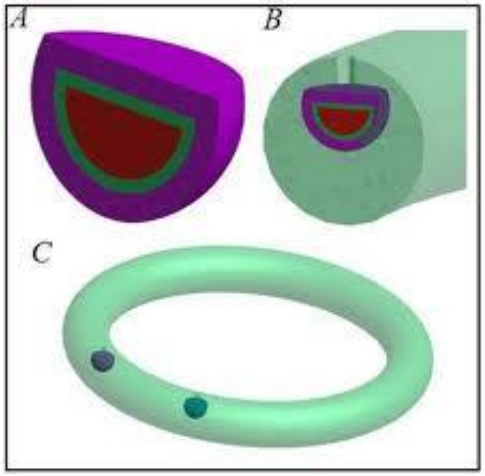


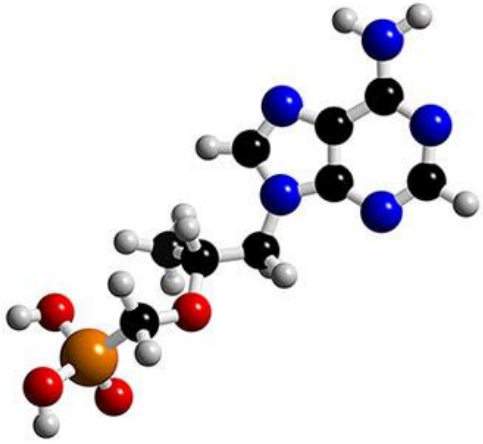


CMPD 167

Other ARV Vaginal Rings in Development

- Tenofovir 90 day polyurethane IVR
  - Johnson et al 2012
  - In vitro characterization and sheep safety/release
- Tenofovir silicone “POD” IVR
  - Moss et al 2012
  - In vitro evaluation and macaque safety and compartment delivery
- Tenofovir + IQP-0528 polyurethane matrix IVR
  - Malcolm et al 2012
- TDF polyurethane reservoir IVR
  - Smith et al 2013
  - Macaque safety and efficacy





Microbicide Film Formulations

- Multiple ARV being evaluated in early stage development as vaginal films
  - Dapivirine, tenofovir, maraviroc, IQP-0528, RC-101
- Phase 1 clinical evaluation of dapivirine film vs dapivirine gel: Ongoing
  - 4 arms (2.5 gm o.5% dapivirine gel, gel placebo, 1.25 mg dapivirine film, film placebo); 15 HIV- women per arm
  - 7 days of product use
  - Grade 2 AEs or higher
  - Systemic and local absorption of dapivirine
  - Biopsy challenge PD assessment
- Combination films and scale up manufacture under investigation

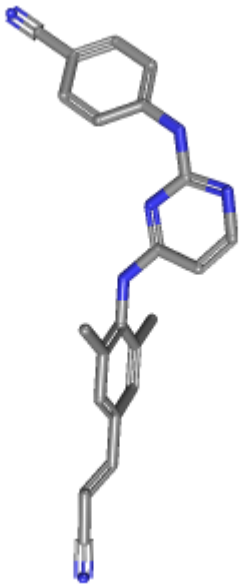
Rectal Microbicides

- Primary Driver: CHARM IPCP program at MWRI (I. McGowan, PI); MTN
- MTN 006: vaginal TNF formulation
- MTN 007: Reduced glycerol TNF gel
- MTN 017: Phase II Safety and Acceptability Study of Tenofovir Gel Reformulated for Rectal Use (pending)
  - Alternating use periods of 1% TNF reduced glycerol gel and oral Truvada in HIV- men
- **Other rectal microbicide work**
  - New Drugs (maraviroc, Griffithsin)
  - Combination drug formulations

Long Acting Injectables:

TMC278 (Rilpivirine):

- NNRTI developed by Tibotec (Janssen) for treatment of HIV infection
  - 25 mg oral tablet (Edurant™) approved in US, EU, Canada
- Highly potent: EC_{50} <0.4 ng/mL 1º HIV isolates
- Long acting nanosuspension administered IM
- 300 mg/mL packaged in glass vials
- Stable at 2-8ºC for at least 24 months
- **Protect in multiple compartments of exposure**
  - **Men and women**
- **Adherence potential of LA formulation**
  - **Higher efficacy potential**



TMC278 Long Acting Injectable:
SSAT 040 Phase 1 Trial

- **Study Design:**
  - HIV negative volunteers, 18-50 yrs, low risk for HIV infection
  - Single IM dose
    - 20 women per arm at 300 mg, 600 mg, or 1200 mg
    - 6 men at 600 mg
  - 1º Objectives:
    - Plasma PK through day 84 post dose
    - PK in genital tract and rectal fluids/tissues
  - 2º Objectives:
    - Safety/tolerability of the 4 different single IM doses of G001
  - Study complete: final data analysis ongoing

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

SSAT ST STEPHEN'S AIDS TRUST

Chelsea and Westminster Hospital NHS NHS Foundation Trust

UNIVERSITY OF LIVERPOOL

BILL & MELINDA GATES foundation

TMC278 Long Acting Injectable:
SSAT 040 Phase 1 Trial PK Results

Trial Summary to Date

Women

Matrix (D 28)	300 mg	600 mg	1200 mg
Plasma	18 ng/mL	54 ng/mL	86 ng/mL
Vaginal Tissue	19 ng/mL	60 ng/mL	61 ng/mL
CVF	29 ng/mL	62 ng/mL	121 ng/mL

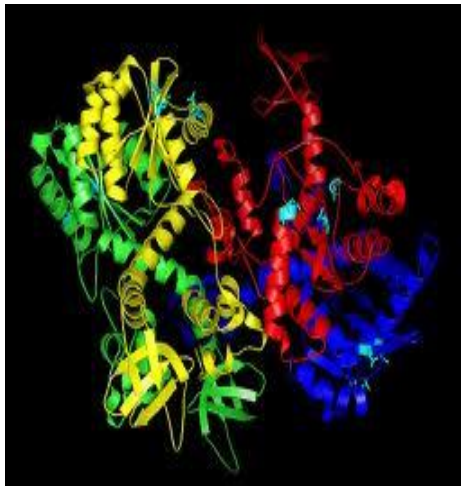
- **Male results (Day 14):**
  - Plasma= 98 ng/mL; Rectal Fluid= 23 ng/mL; Rectal Tissue= 87 ng/mL
- **TMC278 levels are 60-400 fold above EC_{50}**
  - Day 28 VT:plasma ratio with 600 mg SD predicts day 84 tissue levels at ~15-20 ng/mL (50 fold above EC_{50})

Jackson et al, CROI, 2012

Long Acting Injectables:

S/GSK '744

- Integrase inhibitor developed via joint venture between GSK/Shionogi/ViiV
- Evaluated clinically as an oral formulation
  - Generally safe and well tolerated
  - 30 mg/d, 10 days= 2.6 log median reduction in viral load
- Well developed LAP formulation (200 mg/mL) in development for treatment and prevention indications



S/GSK '744 Long Acting Injectable:
Phase 1 PK and Safety

- **Study Design:**
  - 25 women and 31 men in double blind, placebo controlled dose escalation study
  - 7 active arms, one placebo arm
    - 100 mg, 200 mg, 400 mg, 800 mg (2x400 mg) IM
    - 100 mg, 200 mg, 400 mg (2x200 mg) SC
  - Safety: Generally well tolerated with mild-moderate self limited ISR as most common AE. Good systemic safety
    - No drug related grade 3-4 AEs or SAE
  - Plasma results:
    - Prolonged $t_{1/2}$ (21-50 d) relative to oral (30-40 hrs)
    - AUC increase was roughly doe proportional
    - 800 mg IM gave exposure comparable to 30 mg daily oral
      - >20 fold above IC90

Spreen et al, IAS, 2012

S/GSK ‘744 Long Acting Injectable:
Macaque Efficacy Study

- **Study Design:**
  - 8 male macaques received 50 mg/kg at 2 time points 4 weeks apart starting 1 week prior to first virus exposure
    - 8 male placebo macaques
  - Inter-rectal challenge with 50 TCID 50 SHIV162p3 weekly for up to 8 exposures
  - Results:
    - All 8 placebo macaques infected (mean 2 exposures)
    - S/GSK ‘744 treated- no infections at 3 weeks post last challenge (final testing at 10 weeks)
    - Plasma levels comparable to clinical exposure in humans

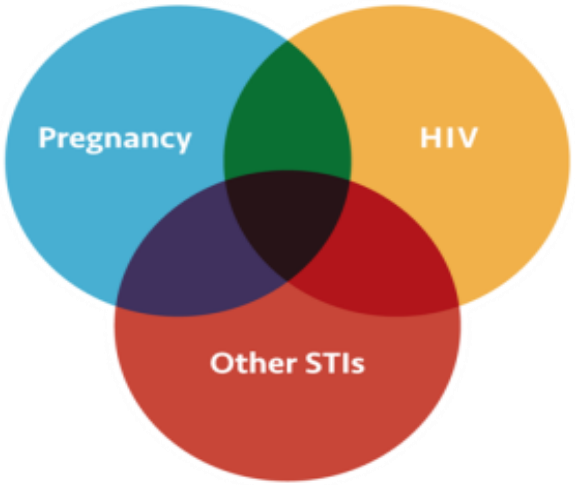
Andrews et al., CROI 2013

Part 1: Summary
New ARV and HIV Prevention Products and Strategies

- New ARV options beyond TNF and dapivirine
  - CCR5 blocker (maraviroc)
  - Integrase inhibition (S/GSK ‘744)
  - Other RTI (rilpivirine, IQP 0528, MIV-150, MIV-160, MC1220, PI)
- New IVR polymers and configurations
  - Silicone, polyurethane, EVA
- New dosage forms in the clinic
  - Vaginal films
  - Long acting injectables

Part 2:
Multipurpose Prevention Technologies

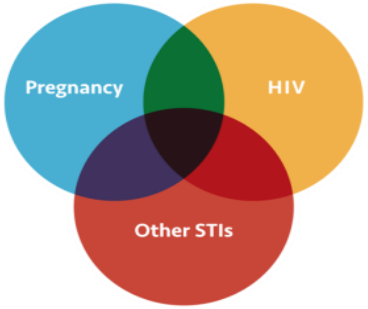
- A single product, configured for at least two SRH prevention indications:
  - **Contraception**
  - **Protection against HIV & other STIs**
  - **Other health benefits**



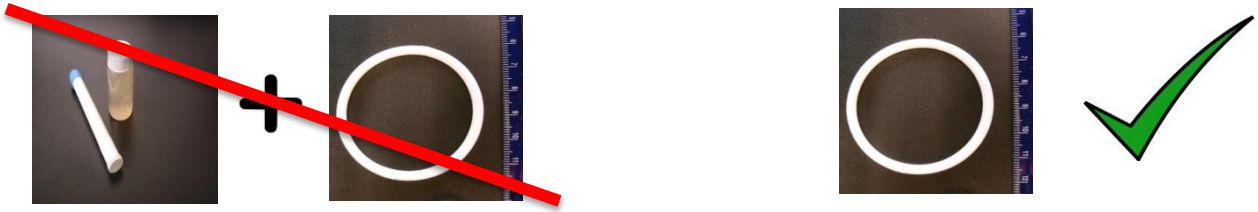
Alternative configurations:

- **Drug: Drug**
- **Drug: Device**
- **Vaccine**

Why Multipurpose Prevention Technologies?



- Greater efficiency in terms of cost, access and delivery of SRH prevention products

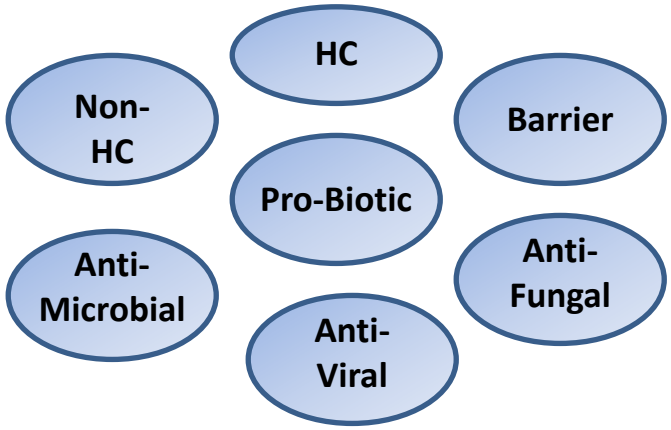


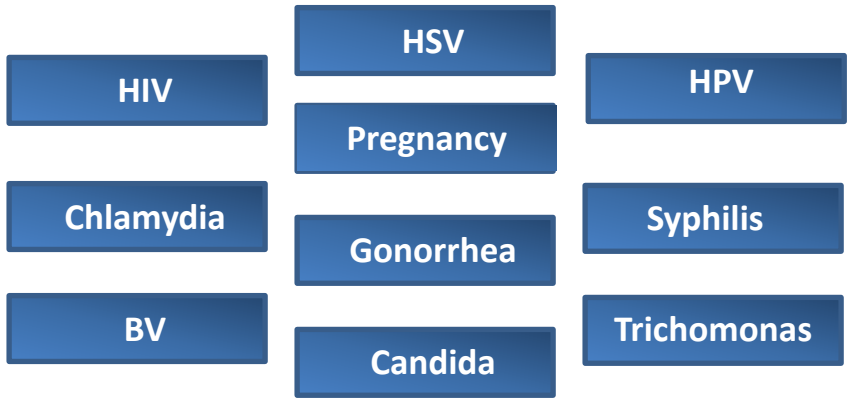
- Capitalize on the demand in populations using one product type to achieve uptake and use of a second “product”

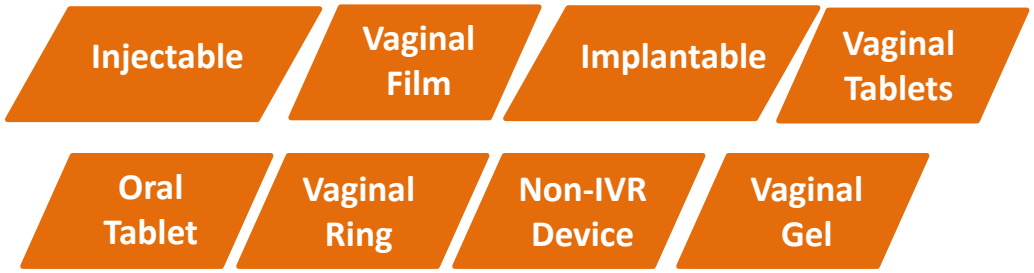
Contraception

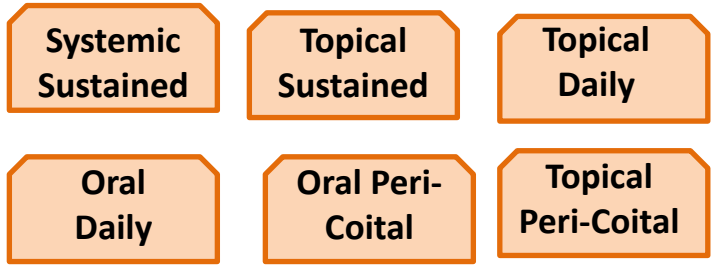
Contraception
HIV Prevention

A Multitude of MPT Options









10 MPT IVR	10 Single Indication IVR	31 HIV Entry Inhibitors
3 On-Demand MPT	12 On-Demand HIV Only	11 Enzyme Inhibitors
2 Barrier MPT	2 Injectable HIV Only	7 Other HIV Inhibitors
23 HC products	2 Lacto-based Products	29 non-HC products

Priority MPT Drugs

Indication	Priority/Comments
HIV Prevention	**Small organic molecule ARV: Potency & Data** -Approved drugs over earlier stage ARV - Long term use safety and resistance potential -Focus on alternatives to RTI (e.g., TNF) ***GAP*** -rProtein/peptides: many options; high cost & risk -HIV drug stigma?
Pregnancy	**Hormone Based: Proven efficacy, wide use** -LNG lead (?); Others to be studied -HC not prioritized for on demand use- Cycle Effects -Potential risk of HIV with specific HC use ***GAP*** -non HC options very early stage ***GAP***
STI Prevention	**Alternatives to broadly neutralizing API** -Minimal number of viable options ***GAP*** -Rapid resistance selection with anti HSV drugs

Priority MPT Dosage Forms

1. **Sustained Release:**
   – **I.e., Vaginal Rings**

2. **Long Acting Injectable**

3. **On-Demand (pericoital)**

GOAL: An MPT of each type for each of the prioritized combination indications

Priority MPT Dosage Forms: **ISSUES**

IVR:

1. Multiple IVR with minor differences in development
   a. Priority: Achieve single P3 lead
   b. Priority: Mitigate risk of current focus on RTI
2. Insufficient data on IVR acceptability and demand
   a. Priority: Objectively quantify both
   b. Address IVR w/ HC use (menses)
3. Robustness and reliability of raw material supply chain
4. IVR polymer compatibility with API limitations
5. Limited number of CMO options

Priority MPT Dosage Forms: **ISSUES**

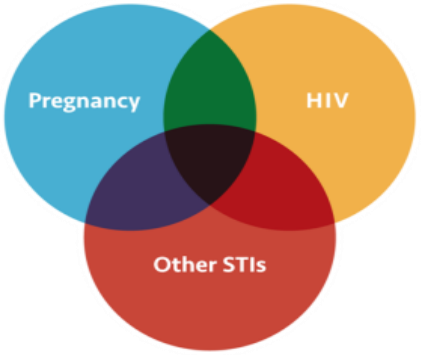
Long Acting Injectable:

1. Co-administration is an acceptable option
2. Equity in duration of effect required
3. Limited area of development: Additional ARV options required
4. Dosage form management:
    a. Necessity of oral run-in?
    b. Addressing long duration drug level “tail”

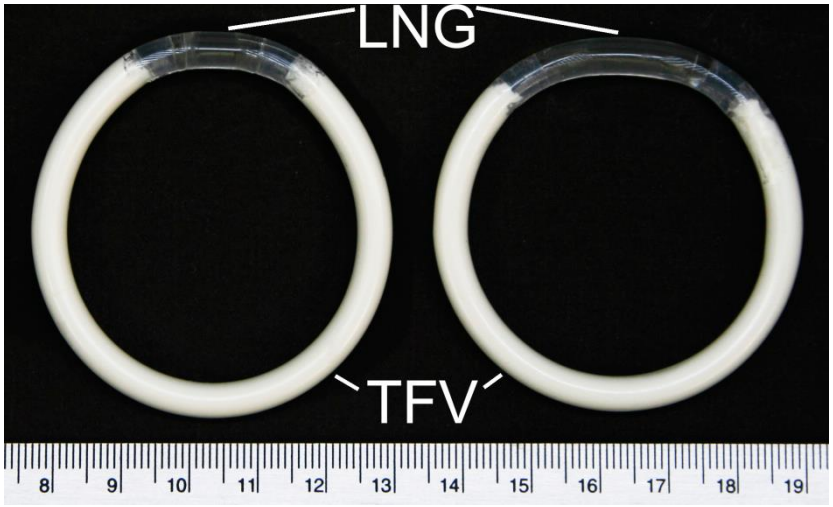
On Demand:

1. Multiple on demand formulations of same API combo not feasible
2. STI and contraception options limited (HC seen as problematic)
3. **Adherence**: Correct and consistent use? True acceptability?
4. Safety and effectiveness of intermittent ARV use

MPT Products in Development: Vaginal Rings- CONRAD, U. Utah

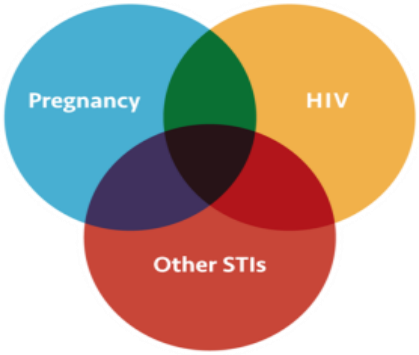


- Prevention of HIV & pregnancy : 90 days
- Segmented polyurethane produced via co-extrusion
- 90 day study in sheep
  - No adverse findings
  - Potentially effective levels of drug release over 90 days
- Phase 1 in Q3, 2013 (planned)
- To be resolved:
  - Storage: LNG crystal formation
  - Manufacture scale up
  - Regulatory: BE to TFV gel?



Courtesy D Friend, CONRAD

MPT Products in Development: Vaginal Rings- IPM



- Prevent HIV/pregnancy: >60 days
- Multiple prototypes in evaluation:
  - EVA core-sheath (Nuvaring)
  - Silicone matrix
  - Silicone core sheath
- Prototype selection: Aprl 2013
  - Optimization
  - Preclin evaluation
  - GMP production

- Phase 1: 2014 (planned)
- Final IVR selection with dapivirine/LNG loads: 2015

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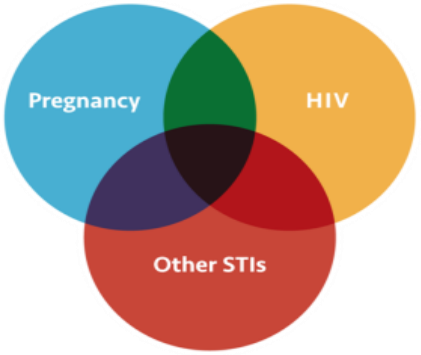
MPT Products in Development: MIV-150 Products- Pop Council



Combinations of MIV-150 (NNRTI), Zinc acetate, LNG, carrageenan in IVR or on-demand formulations

- Combination dependent prevention of HIV, HSV, HPV, pregnancy
  - Supported by animal data (HIV: macaque; HPV, HSV: mouse)
- Primary focus: Gel and IVR
- Planned clinical studies: 2016

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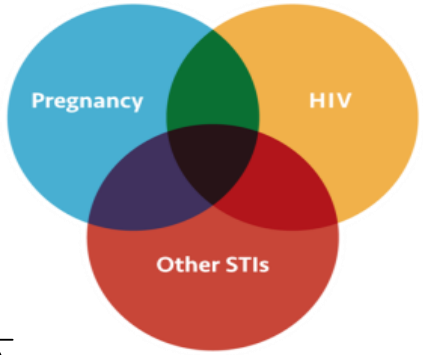
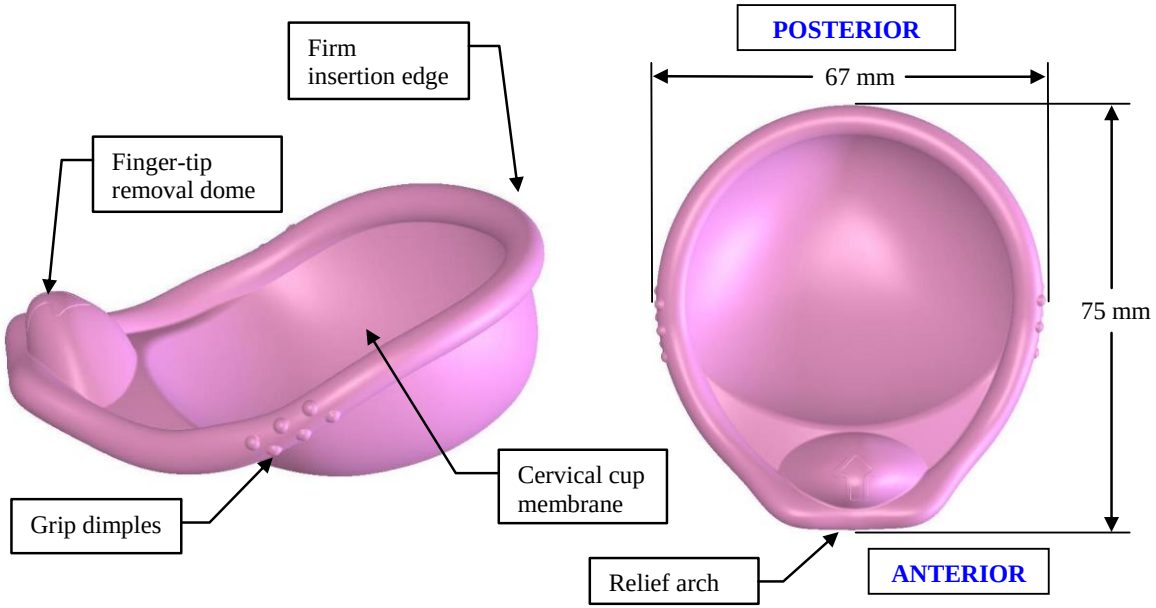
MPT Products in Development: Barrier- Microbicide- PATH

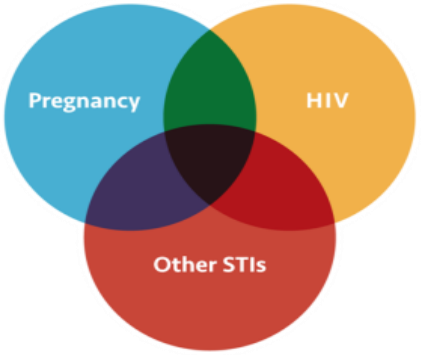




- SILCS diaphragm administered with microbicide gel
  - Entering Phase 1 evaluation with TFV 1% gel in 2013
  - Developing a contraceptive TFV 1% gel in parallel
- SILCS diaphragm that releases a microbicide
  - Development has proven challenging

Courtesy D Friend, CONRAD

MPT Products in Development: Long Acting Injectables



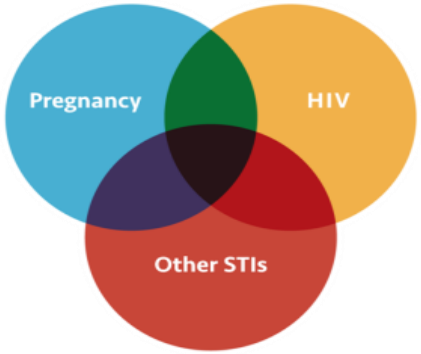
- Co-administration Strategy:

Rilpivirine
S/GSK '744

Depo Provera

Cyclofem

Other MPT Product/Technology Options:



Implants
Lactobacillus GMO (Osel)
Verselle Gel Delivery (FHI 360)
Broad Spectrum Natural Products
Proteins/Peptides
Non-Hormonal Contraceptives
Vaccines

Other MPT Priorities, Gaps and Comments:

Regulatory:

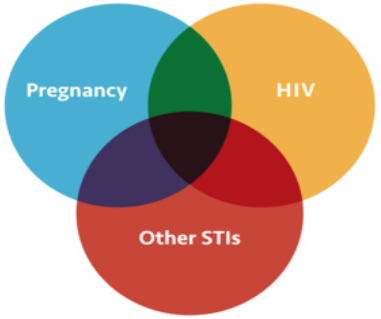
1. Engage regulators early; Familiarity at local regulatory level
2. "Bridging" dosage forms via BE studies: Potential challenges

Social/Behavior:

1. Critical to study MPT in adolescent populations
2. MPT needs and issues will differ regionally

Access and Delivery:

1. Proof of demand (**not need**) early in development
2. Accurate and relevant forecasting
3. Policies and practices of the procuring entity
4. Manufacturability and automation
5. Supply chain (raw materials, finished product)
6. Delivery channels (**last mile!**)
7. Partnering options



Thank You and Questions